Press Release

NOTCH: a therapeutic target in 30% of lung cancers

Milan, 14 December 2009 – The **Notch** receptor is a protein that is known to be involved in the formation and development of cancer. Until today, this receptor was known to be involved in certain types of leukaemia, but its role in solid tumours, the most common group of human cancers, was unknown. Now a team of scientists and clinicians who work at the **IFOM-IEO Campus** in Milan, and who are affiliated with **IFOM** (FIRC Institute of Molecular Oncology), **IEO** (European Institute of Oncology) and the **University of Milan,** have uncovered a role for Notch in lung cancer. The study, which will soon be published in scientific journal **PNAS,** demonstrates that Notch is functionally altered in more than one third of lung cancers.

In many of these cancers, altered Notch activity is caused by the loss of expression of a biological antagonist of Notch, a protein called Numb that has previously been shown to be tumour suppressor gene in breast cancer by the same group of researchers. “Previously,” – explains **Pier Paolo Di Fiore,** Director of the “Endocytosis, Signalling and Cancer” research programme at IFOM, Full Professor of General Pathology at the Department of Medicine, Surgery and Dentistry, University of Milan, and one of the two main authors of the study – “we observed that the loss of regulation of Notch by Numb was an important mechanism in the development of breast cancer. Now, we know that this same mechanism is also relevant to lung cancer.” “However,” – continues Di Fiore – “the novelty of our recent study rests in the fact that in approximately 10% of lung cancers altered Notch activity is caused by mutations in the Notch gene. These mutations primarily affect the mode of activation of Notch, causing self-activation of the receptor, independently from external signals. These genetic lesions have already been detected in some types of leukaemia, but never in solid tumours.”

That is not all: the researchers, using tumour cells from lung cancer patients, have already identified a therapeutic strategy to inhibit tumour growth driven by Notch. This discovery opens up new avenues in the development of clinical strategies to combat lung cancer, which is the leading cause of cancer death in industrialized countries. "We have identified Notch as a molecular target that is critical to the formation and progression of lung cancer.” – explains **Pier Paolo Di Fiore** – “We have also demonstrated that drugs capable of inhibiting the transcriptional activity of Notch in tumour cells have an anti-proliferative effect on cancer cells.”

“Through a retrospective study on biopsy samples, we established that lung cancer patients with altered Notch activity have a less favourable clinical outcome,” explains **Giuseppe Viale**, Director of the Division of Pathology at IEO, Full Professor of Pathological Anatomy at the Department of Medicine, Surgery and Dentistry, University of Milan, and co-author of the study. “The identification

of Notch as a prognostic indicator and as a predictor of response to treatment with targeted drugs is extremely important for the translation of our discovery to the clinic," – says IEO researcher **Salvatore Pece,** also Assistant Professor of General Pathology at the Department of Medicine, Surgery and Dentistry, University of Milan, and the second main author of the study – "In the near future it will be possible to design clinical trials to test the efficacy, in lung cancer patients, of drugs (**gamma secretase inhibitors**) that specifically inhibit Notch activity and that block proliferation of tumour cells."

The study will be published in the next issue of PNAS (Proceedings of the National Academy of Sciences) and was made possible mainly thanks to support from the **Italian Association of Cancer Research (AIRC),** as well as grants from the **Italian Ministry for Education, Universities and Research (MIUR)**, the **Italian Ministry of Health**, the **European Community,** the **Ferrari Foundation**, the **Cariplo Foundation** and the **Monzino Foundation**.

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